REMARKS

A. Status of the Claims

Claims 1-28, 30, 31, 33-67, 73, 76-99, 105-109, and 111-125 are pending in this application. Of these claims, claims 2-23, 28, 30, 31, 36-67, 74, 78-98, 109, 111-113, 118, and 122 are withdrawn from consideration. Accordingly, claims 1, 24-27, 33-35, 99, 105-108, 114-117, 119-121, and 123-125 are presented for examination.

Claims 123 and 125 are objected to under 37 C.F.R. § 1.75 for allegedly being a substantial duplicates of present claims 99 and 24, respectively.

Claims 1, 24-27, 33-35, 99, 105-108, 114-117, 119, 121, and 123-125 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over U.S. Patent No. 6,573,299 to Petrus ("Petrus") in view of an abstract of an article entitled "Connective tissue biochemistry of the aging dermis. Age-related alterations in collagen and elastin", by J. Uitto, Dermatol. Clin. 1986 Jul; 4(3):433-46 ("Uitto").

B. Withdrawn Claims

In the June 15, 2007 Office Action, the Examiner withdrew claims 28, 109, and 113 for being directed to non-elected subject matter. In response, Applicants respectfully note that the MPEP § 806.04 states that "an allowable generic claim may link a reasonable number of species embraced thereby". The Examiner appears to take the position that "one" is the maximum reasonable number of species by limiting the examination to zinc citrate only. However, Applicants respectfully submit that this position would be inconsistent with the MPEP, as well as 37 C.F.R. § 1.146, which provides for the examination of a "reasonable number" of

species. Accordingly, Applicants respectfully request the examination of withdrawn claims 28, 109, and 113.

C. Objections to Claims 123 and 125

The Examiner objects to claims 123 and 125 for being substantially identical to claims 99 and 34, respectively, to the extent that they depend from claim 24. In response, Applicants have amended claims 123 and 125 so that they no longer depend from claim 24.

Applicants respectfully request reconsideration and withdrawal of this objection to the claims.

D. Applicants Claims Are Patentable Over the Cited References

Applicants respectfully traverse the rejection of claims 1, 24-27, 33-35, 99, 105-108, 114-117, 119, 121, and 123-125 under 35 U.S.C. § 103(a), for allegedly being unpatentable over Petrus, in view of Uitto. As discussed in detail below, the traversal is based on at least the following four reasons: (1) Petrus teaches away from the claimed zinc concentration ranges; and (2) the combination of references fails to teach or suggest all of the claim elements; (3) Applicants have met the evidentiary burden for showing that the unexpected effects seen in the Examples set forth in the specification generally applies to the claimed subgenus; and (4) the industry recognition enjoyed by Applicants' Zn-based commercial products is an important secondary consideration of non-obviousness.

For at least these reasons, the rejection is improper and should be withdrawn. See MPEP §§ 2145, 2143.03, 2141(III).

1. Petrus Teaches Away from the Claimed Ranges

As an initial matter, Applicants note that Petrus is directed to treating disorders associated with the aging eye. These disorders include orbital disorders such as glaucoma, cataracts, diabetic retinopathy and age-related macular degeneration (AMD) [see Petrus, col. 2, line 38 to col. 4, line 34], as well as age-related changes to eyelids, such as dry skin, wrinkles, keratoses, age spots, and pigmented skin lesions [Petrus, col. 2, line 30-32]. According to Petrus, a primary cause of these disorders is inflammation. In fact, Petrus expressly states that "[i]nflammation accelerates the aging process and is believed to be responsible for many of the changes that occur in the aging eye" [Petrus, col. 9, lines 29-31]. To prevent or to treat such conditions, Petrus suggests the use of anti-inflammatory compounds, including N-acetylcysteine, ascorbyl palmitate, ascorbic acid, alpha-lipoic acid, glutathione, methyl-sulfonyl-methane, zinc compounds, and aloe vera extract [Petrus , col. 8, line 45 to col. 14, line 34].

As noted in Applicants' previous response dated March 30, 2007, one aspect of Applicants' invention is the recognition that excessively high levels of zinc may cause irritation and sloughing of the skin [see, e.g., Example 1]. Skin irritation is characterized by local inflammation of the epidermis or the outer dermis [see, e.g., the Wikipedia article on contact dermatitis, available at http://en.wikipedia.org/wiki/Contact_dermatitis, a copy of which has been provided with this response]. Thus, Example 1 of Applicants' specification teaches that the application of excessive amount of zinc to the skin leads to skin inflammation.

In contrast, Petrus fails to recognize that zinc compounds can cause skin irritation at all. To the contrary, Petrus repeatedly characterizes zinc compounds as "anti-inflammatory" [Petrus, col. 12, lines 10 and 44]. Furthermore, Petrus teaches that "zinc is virtually non-toxic"

[Petrus, col. 12, line 53]. Thus, a person of ordinary skill in the art, upon a faithful reading of Petrus, would seek to *increase* the amount of zinc compound in preparing a composition for the aging eye, because of zinc's purported "anti-inflammatory" effect and its purported non-toxicity.

An analysis of Petrus' discussion of zinc compounds further supports the view that Petrus teaches away from the claimed zinc concentration ranges. Petrus states that "[z]inc is also a very potent inhibitor of nitric oxide synthase (NOS)", and explains that "[t]he overexpression of NOS may result from increased levels of tumor necrosis factor-a (TNF-α), IL-1β, and other proinflammatory cytokines" [Petrus, col. 13, lines 16-17, col. 7, lines 51-53]. Thus, Petrus teaches that zinc may be used to inhibit NOS expression through the suppression of proinflammatory cytokines. Towards the goal of suppressing NOS formation, Petrus states that "[t]he suggested [zinc] topical dosage range of the present invention is 10 to 20 mg per day" [Petrus, col. 13, lines 19-21]. However, this topical zinc dosage range leads to concentration ranges that are ***higher*** than those recited in Applicants' claims, as Applicants previously noted on pages 34-35 of their March 30, 2007 paper. Further, Petrus states that zinc is "anti-inflammatory", "virtually non-toxic", and a "very potent inhibitor of nitric oxide synthase", which would, if anything, strongly suggest ***increasing*** the amount of zinc in a composition for the aging eye.

Applicants further note that Petrus' statement that "[t]he bio-affecting agents will vary from about 0.1% to 40% of the total composition…" [Petrus, col. 6, lines 61-62], which applies generally to all of the bio-affecting agents discussed in Petrus, does not render Applicants' claimed zinc concentration ranges obvious. Indeed, given the large number of bio-affecting agents disclosed by Petrus, countless compositions containing different bio-affecting

agents and/or different amounts of bio-affecting agents are embraced by Petrus' specification. Accordingly, Applicants' claimed zinc concentration ranges, which are not even explicitly disclosed in Petrus, represent a "needle-in-a-haystack" when considered in view of Petrus' specification (or the Examiner's combination of Petrus and Uitto) and are not obvious. See, e.g., *In re Luvisi,* 52 C.C.P.A. 1063, 1068 [holding that the claimed borate compositions were a "needle-in-a haystack" in view of the prior art, and therefore were not obvious over the prior art].

2. The Combination of References Does Not Teach or Suggest the Zinc Concentration Ranges of the Claimed Invention

In the last three Office Actions, the Examiner has rejected Applicants' claims over Petrus, in view of various secondary references. However, nowhere has the Examiner shown that Petrus, alone or in combination with any of the secondary references, teaches or suggests the claimed zinc concentration ranges. At best, the Examiner merely relies upon a statement in Petrus that "[t]he concentration of the bio-affecting agents in the composition can also vary greatly and will be dependent upon many factors, e.g., type, bioavailability, potency, surface area to which it is applied, composition used and the amount of penetrating agent used" [see page 7 of the Office Action, citing col. 6 lines 56-60 of Petrus]. On the basis of this statement, the Examiner concludes that "Petrus expressly contemplates variations in dosage amounts" [page 7 of the Office Action] and that it "would not have required undue experimentation" by a person of ordinary skill in the art to arrive at the claimed zinc concentration ranges [Office Action, page 7].

The Examiner's analysis, however, disregards the remainder of the specification of Petrus, which provides several alternatives to zinc for treating the aging eye. For example, to treat wrinkles, Petrus states that alpha-lipoic acid may be used [Petrus, col. 10, line 63 to col. 11, line 22]. Moreover, to treat inflammation associated with various orbital disorders, Petrus states that N-acetyl cysteine, ascorbyl palmitate/ascorbic acid, alpha-lipoic acid, glutathione, methyl-sulfonyl-methane, or aloe vera extract may be used as anti-inflammatory agents [Petrus, col. 8, line 45 to col. 14, line 34]. Furthermore, to treat glaucoma by inhibition of nitric oxide synthase, Petrus states that arginine-based analogues, flavoprotein binders, ornithine and its derivatives, tetracycline, L-canavanine, citrulline, redox dyes, calmodulin binders, heme binders, resveratrol, tetrahydropterin analogs, and depleters of biopterin, may be used in addition to zinc compounds [Petrus, col. 7, line 45 to col. 8, line 44].

There is no teaching or suggestion in Petrus or Uitto to favor zinc compounds over any other disclosed class of compounds for treating wrinkles, inflammation, or for suppressing nitric oxide synthase expression. Thus, the Examiner's contention that it "would not have required undue experimentation" to arrive at Applicants' claimed zinc concentration ranges, despite the myriad possible compositions embraced by the proposed combination of Petrus and Uitto, is, at best, impermissible hindsight reasoning. Accordingly, the rejection of Applicants' claims for being unpatentable over the combination of Petrus and Uitto should be withdrawn. See MPEP § 2145.

Also, it is well established that obviousness cannot be predicated on what is not known at the time the invention is made, even if the inherency of a certain feature is later established. See *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955(Fed. Cir. 1993). Here, it is

indisputable that Petrus and Uitto fail to recognize any deleterious effect caused by high zinc concentrations. Moreover, based on Petrus, it would be impossible to conclude whether zinc compounds cause irritation, given that Petrus teaches combining zinc with various anti-inflammatory compounds. In other words, the other anti-inflammatory compositions in Petrus' compositions would be expected to mask the inflammation associated with the skin irritation caused by Petrus' high zinc concentrations. This situation is illustrated, for example, by the compositions in Examples 1 and 2 of Petrus, which involve the combination of 2% zinc lineolate with no less than five other compounds acknowledged by Petrus to be anti-inflammatory agents (*viz.*, methyl-sulfonyl-methane, ascorbyl palmitate, alpha-lipoic acid, glutathione, and aloe vera). As Applicants noted in their March 30, 2007 response, a concentration of 2% zinc lineolate is above Applicants' claimed zinc concentration range, which concentration range does not cause skin irritation or sloughing. Thus, if the zinc lineolate at this higher concentration caused skin irritation, a practitioner using the compositions of Petrus would not be aware of the irritation, given the presence of five anti-inflammatory agents.

That is not to say, however, that the zinc concentrations in Petrus' compositions can be freely increased to boost elastin production, as long as sufficient amounts of anti-inflammatory agents are added to compensate for the skin irritation caused by zinc. As Applicants demonstrate in Example 9, when the zinc concentration is very high, elastase activity is induced by zinc. When this happens, the result is a breakdown of elastin (a condition known as "elastosis"), which leads to less elastic skin, the antithesis of a person seeking to treat wrinkled skin.

None of these effects are recognized by Petrus, or the combination of Petrus and Uitto. Further, the Examiner has not shown that it was recognized in the art, at the time of the invention, that high zinc concentrations would cause irritation and sloughing.[1] Accordingly, Applicants' claims are patentable over the cited references, and the Examiner's rejection of the claims under 35 U.S.C. § 103(a) should be withdrawn.

3. Applicants' Have Met the Evidentiary Burden of Showing Unexpected Effects for the Claimed Sub-genus

In the first full paragraph of page 9 of the Office Action, the Examiner contends that Applicants' results as illustrated in Examples 1 and 9 "do not provide a basis for concluding that the claimed subject matter would not have been obvious because the results are limited to a distinctly different zinc salt (i.e., zinc acetate vs. zinc citrate)" [Office Action, page 9, lines 6-8]. However, as the Examiner herself notes, Federal Circuit case law does not restrict the claims of an Applicant to only what has been actually reduced to practice:

> [e]vidence that the compound or composition possesses superior and unexpected properties in one of a spectrum of common properties can be sufficient to rebut a prima facie case of obviousness [citing *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)]. For example, a showing of unexpected results for a single member of a claimed subgenus, or a narrow portion of a claimed range would be sufficient to rebut a prima facie case of obviousness if a skilled artisan 'could ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof.' [citing In re Clemens, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)] (emphasis added).

[1] Applicants further note that even if the Examiner were to find a reference teaching away from using high zinc concentrations, such a reference would be incompatible with Petrus teaching that zinc is "anti-inflammatory" and "virtually non-toxic". Accordingly, it would be improper to combine such a reference with Petrus for the purpose of a rejection under 35 U.S.C. § 103(a).

In the instant case, Applicants have used zinc acetate to demonstrate that high zinc concentrations can lead to irritation and sloughing. As shown in Applicants' Examples, the data are discussed in the context of Zn cation concentration alone. For example, the zinc acetate stock solutions described in Example 1 are referred to in terms of the Zn^{++} ion concentration. Similarly, Tables 1-4, as set forth in Examples 2-4, all report results as a function of the Zn^{++} ion concentration. Accordingly, one of ordinary skill in the art, upon reading Applicants' specification, would know that it is the Zn cation concentration, (and not the counterion concentration) that is responsible for the observed effects. Thus, one of ordinary skill in the art would be able conclude, on the basis of Applicants' specification alone, that the results of zinc acetate are probative of the behavior of zinc citrate.

4. Secondary Indicia of Non-Obviousness

As noted above, Applicants' claims are not obvious over the cited references for several reasons: (1) Petrus teaches away from the claimed Zn concentration ranges; (2) the combination of references fails to teach or suggest all of the elements of the claimed invention; and (3) Applicants have provided evidence to allow a person of ordinary skill in the art to conclude, based on Applicants' data for zinc acetate, that similar results would be observed for zinc citrate.

In this section, Applicants turn to the industry recognition enjoyed by Relastin™, a line of Zn-based commercial products developed by Applicants, which products are covered by one or more of the pending claims in the instant application. Since the launch of Relastin™ on July 7, 2006, the product has enjoyed considerable industry recognition and praise from many

different reviewers. Notably, Relastin Eye Silk won Allure Magazine's 2007 Editor's Choice "Best of Beauty" Award in the category of "Antiwrinkle Eye Creams", after independent testing and retesting against other competing products [see accompanying excerpt from Allure Magazine]. This recognition by one of the premiere beauty magazines in the industry provides strong secondary evidence confirming the non-obviousness of Applicants' invention.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 103720-105089US1. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 103720-105089US1.

Respectfully submitted,
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